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Protection of Newborn Hearts:
The Effect of Extracellular Calcium on the Development of Irreversible Ischemic Injury

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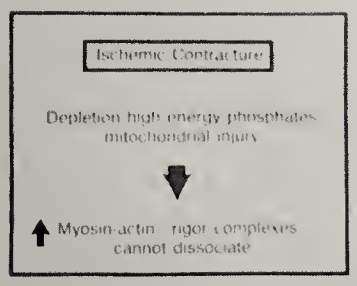
Introduction

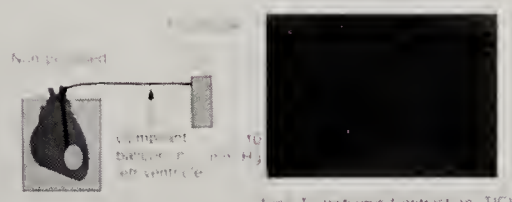
Previous work in this laboratory demonstrated a greater susceptibility of the newborn myocardium when compared to adult myocardium to damage induced by global ischemia as measured by time to ischemic contracture (TIC), an accepted indicator of irreversible cellular damage. These age-related differences in myocardial structure and metabolism have been pertain to calcium handling. Findings such as the rapid rise in the rate and sensitivity of the calcium channels in the newborn rat heart [illegible] has led to the postulate that the newborn myocardium may be more sensitive to extracellular calcium. In adult hearts, changes in extracellular calcium concentration do not affect the time to onset of peak ischemic contracture but do change the peak pressure generated in the damaged heart. To date little is known as to the effects of extracellular calcium on the ischemic newborn myocardium.

Hypothesis

If the newborn heart is truly more sensitive to extracellular calcium than the adult, then changes in extracellular calcium concentration will influence the ischemic contracture of newborn myocardium to a greater extent than observed in adults. Such an occurrence may provide an explanation for the increased sensitivity of newborn heart [illegible]

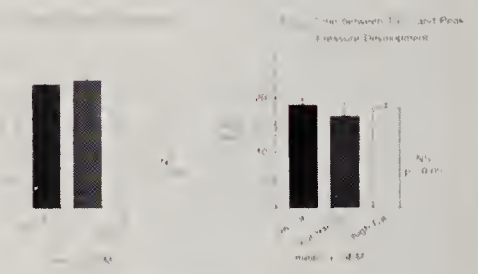


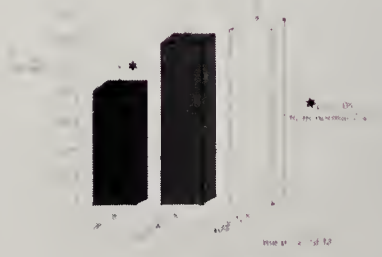
Materials and Methods



* Myocardial damage induced by ischemia was assessed by measuring the time to onset & peak ischemic contracture. Results were analyzed by ANOVA/TUKEY and p [illegible] .05 was considered significant.

Results





Conclusion

For newborn myocardium, the availability of extracellular calcium does not significantly influence either the onset or duration of contracture due to ischemia, but does play a role in determining the peak pressure generated. This suggests that differences between neonatal and adult vulnerability to ischemic myocardial damage cannot be explained by differences in sensitivity to extracellular calcium alone.

1987
University of Toronto
Faculty of Medicine
Undergraduate Medical Student Research Day
Second Annual Meeting Abstracts

* * *

December 1
Medical Sciences Building
Toronto, Ontario

Message from the Dean

The Medical Research Day is a remarkable event. It is a highly significant event in the day to day goings-on of a medical school. It brings together the excellent research work that students have participated in and have created as a result of their summer fellowships and additional commitments to research.

The full spectrum of research that is demonstrated was truly laudatory, covering the most biological to highly applied clinical work in hospitals and in the community. This indeed is a harbinger of the career pathways that students may choose in the future. Having a personal sampling of participating in research usually gives one the inescapable taste to be at the beginnings of new knowledge; to have an understanding of how knowledge is developed; and where many of our practices in medicine came from.

Today's research is always tomorrow's medicine and the students who participate in research form part of the framework of future knowledge that will be used by others in practice. I hope that there will also be an encouragement to embark on a future research career.

The world is expanding rapidly, medicine is changing at an incredibly brisk pace, and the developed countries that participate in this research very quickly have the best medicine and also have the best health care systems and the best economic way of life. To be in research is to enjoy the frontier and I hope that many of you will take it up.

John H. Dirks, M.D.
Dean

Student Research Day: A Tradition in the Making

Niall Byrne, CSME, Faculty of Medicine

The University of Toronto medical school sees itself as a major research institution and has endeavoured to encourage students, through its MD/PhD and UPMS programmes, to engage in research. Thus, when Michael Paré approached me I realized his idea of holding a Student Research Day was an excellent one. The idea was simple: organize a forum that allows students to manifest their research efforts, stress the notion that research is not so much a serious cerebral exercise as it is an activity of fun and discovery and promote research among medical students.

Michael and I decided to go ahead and do it. Our first job was to storm the bureaucratic walls of the great institution seeking support and help. In the event, we met no resistance. Deans, staff and students agreed it would be a worthwhile activity.

The first year (1986) was both successful and disastrous. It was successful from the point of view of the quantity of submissions (59) and the quality of presentations (9). It was disastrous from an attendance point of view. Except for a few staff and the presenting students only a small audience attended. The mistake we made was twofold: Instead of attracting students, we put them off by preselecting 9 papers; moreover, we obliged the selected few to present their research much like experts at a scholarly conference.

We learned. With good advice from Drs. Bayliss, Murray, Salerno, Taylor and Whiteside we found the right formula to achieve the original objectives. No preselection was done. Every student who submitted an abstract was encouraged to offer a poster at Research Day. The result was 57 posters and a large attendance at the 1987 second annual day. Also, because of this number of abstracts submitted (14) dealing with the central nervous system we decided to put on a Symposium titled "The Brain". Dr. Peter Ashby selected 4 of the abstracts for presentation and prepared the students to present their research. The symposium was well attended and it was generally felt that the quality of presentations was high and the content informative.

To acknowledge the importance of Student Research Day, the Medical School supported and funded three incentives for those who participated:

1. Elective credit, recorded in transcripts.
2. Income from the George Brown Memorial Scholarship fund to chosen winners, and recorded in transcripts.
3. A celebration dinner following the presentations.

The 1987 Research Day was a watershed in the sense that a general consensus emerged to establish the event as a continuing expression of undergraduate student research. To many of our faculty it was a surprise that so much research by students was being accomplished. The amount and quality of student research opens up a new issue as to whether a more structured approach, such as a research stream in the undergraduate curriculum, is practical and appropriate. Obviously Research Day, whatever its curriculum consequences, is here to stay. A traditon is in the making.

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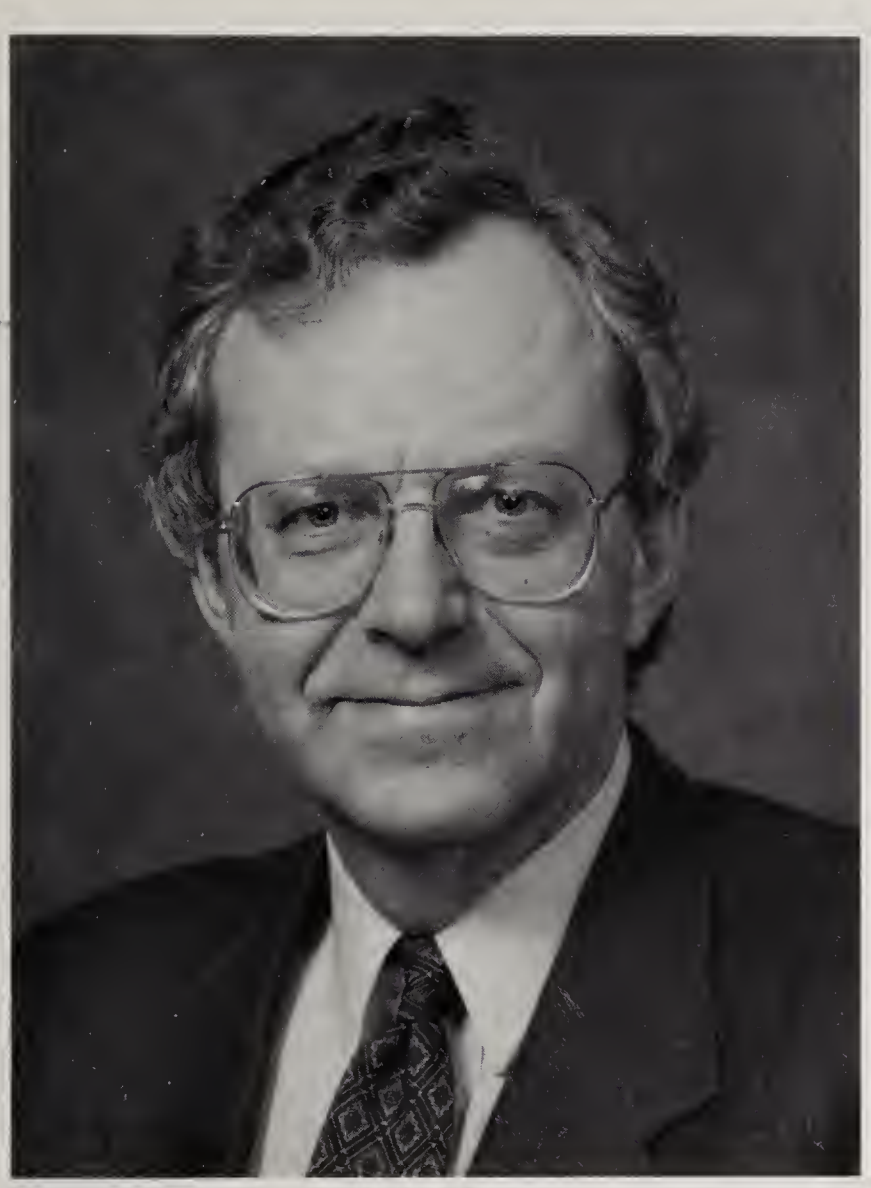
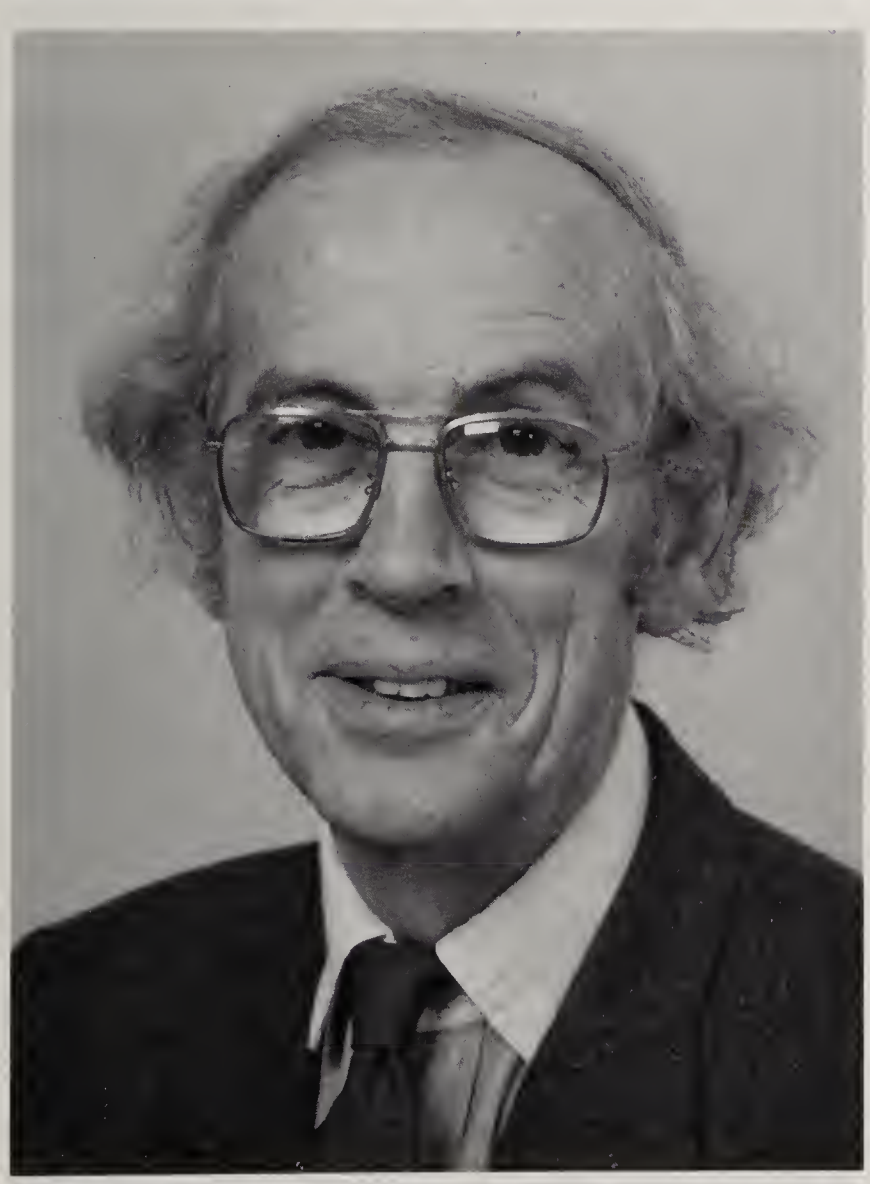


John H. Dirks, M.D. Dean



Niall Byrne, CSME, Faculty of Medicine

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Cover illustration: Winning poster by John S. Ikonomidis.
Photographed by Dave Mattice.

Research Day — 1987

C. Whiteside, M.D., Assistant Professor of Medicine

The second annual undergraduate Medical Research Day was a great success objectively measured by a two to three-fold increase in participation of students and faculty members since 1986. The innovative poster session planned by Niall Byrne and his student committee, facilitated this enhanced participation. The presentations in the neuroscience symposium coordinated by Peter Ashby were of top academic calibre and stimulated many thoughtful questions by the student audience.

Undergraduate Research Day was born in the mind of Michael Paré in 1986 a second year medical student, who wondered why more emphasis wasn't placed on undergraduate medical research endeavours at U of T. He put forth evidence that other (smaller) Canadian medical schools did recognize its importance and had initiated activities such as time set aside in the curriculum for the students to have an opportunity to share their accomplishments and also be rewarded for excellence. Although there was approval in principle for his suggestion, it was Niall Byrne, presently the Director of the Centre for Studies in Medical Education, who responded with enthusiasm. My own participation has led me to reflect on the relevance of undergraduate research and in particular the events of the undergraduate Research Day to our Faculty. Specifically I have focused on the process of learning.

First, let me explain what I have learned. Witnessing the outcome of Michael's question I understood more fully the potential impact of questions raised by our students. These individuals, who in four short years become practicing physicians, are seriously dedicated to a career in medicine. This is made clearly evident by the extremely stiff entrance criteria they meet to gain admission to medical school. It is a legitimate concern about their own learning that stimulates critical and usually constructive assessment. As faculty members caught up in our own clinical and research careers, it is easy to minimize our roles as undergraduate educators. Yet, within our school there are many staff who recognize the value of student analysis and respond positively. Let us not forget that the annual undergraduate Research Day was primarily a medical student initiative.

Research Day is also a sign of curriculum renewal. This concept can be described best by what, and how, the student participants have learned. As I thought about this, a question came to mind. Every year I ask the medical students in my year III clinic group what it is that they dislike most about their medical school learning experience. The resounding answer is — "memorizing thousands of facts for multiple choice exams." As a former medical student at U of T I recall feeling exactly the same. It is not just that this task is boring and frequently perceived as irrelevent. Rote memorization is a real 'mind turn-off'. In contrast, the medical students who become involved in a research project, with the guidance of their supervisors, experience learning with a 'turned-on mind'.

The evolution of this phenomenon is quite simple. Put yourself in the position of a medical student beginning a summer research project. Presented with a question, or better yet after designing your own, you first explore the literature and then define a useful hypothesis. Next you set out an experimental design to address your question. The experiments are challenging and demand ingenuity. You subject your data to rigorous statistical analysis. Then comes the realization that you have generated new scientific information and experience the thrill of discovery. The hard work doesn't stop here. Next is the abstract deadline, the preparation for the Research Day presentation, not to mention the writing of the scientific article. All of this is far more time consuming than you had ever imagined. But there is something about it that is more satisfying than the usual memory-laden learning experience in medical school. You have participated in a self-motivated creative process.

There is another dimension to learning stressed by Michael's suggestion. It is revealed by the student presentations at Research Day. Again place yourself in the shoes of the student presenting his or her work. Suddenly, your role as a medical student has been reversed. In a clear and concise manner you now have to educate both colleagues and faculty members about your experimental analysis and conclusions. You open yourself to critical appraisal and it becomes evident that in order to

(continued on S-32)

C. Whiteside, M.D., Assistant Professor of Medicine

Editorial

Catherine Birt, Michael Paré and Raymond Ng
Editors-in-Chief

The following research abstracts are from the second annual Undergraduate Medical Student Research Day (UMSRD). This Research Day was initiated in 1986 by Dr. Niall Byrne (Division of Studies in Medical Education) and Dr. Robert Murray (Department of Biochemistry). The Day was designed as a forum for students who have engaged in medical research to present their work in a format similar to that of a scientific meeting. The second annual Research Day way also organized by Dr. Niall Byrne and was highlighted by an after dinner speech by Dr. Catherine Whiteside of the Department of Medicine. In her presentation Dr. Whiteside emphasized the importance of research opportunities in the undergraduate medical programme.

The Editors of the Journal, on behalf of the entire undergraduate student body, extend their thanks — not only to the above mentioned faculty members — but also to Dean Dirks and to the entire Faculty of Medicine for their continued support for UMSRD. We also gratefully acknowledge the Faculty of Medicine's financial contribution from Dean Dirks, Dean Hollenberg and Dean Sellers that has made this abstract supplement possible.

Robert Murray, M.D., Faculty of Medicine

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GEORGE BROWN MEMORIAL AWARD FOR RESEARCH ACCOMPLISHMENT RECIPIENTS

IMPROVED MYOCARDIAL PROTECTION WITH GLUTAMATE-ASPARTATE BLOOD CARDIOPLEGIA

D. Young*, P.L. Birnabum, R.D. Weisel, M.M. Madonik, J. Ivanov, C. Finkle, D.A.G. Mickle
Division of Cardiovascular Surgery and the Department of Clinical Biochemistry, Toronto General Hospital, Toronto, Ontario

Previous investigations demonstrated transient ventricular dysfunction and delayed myocardial metabolic recovery after elective coronary artery bypass graft (CABG) surgery. Our animal studies suggested that myocardial metabolic recovery was delayed after ischemia and cardioplegia because critical tricarboxylic acid cycle (TCA) intermediates were diminished inducing mitochondrial dysfunction.

Hypothesis: The addition of the TCA intermediates to the heart during cardioplegic arrest may improve metabolic and functional recovery.

Methods: Twenty-two patients undergoing elective CABG were randomized to receive either blood cardioplegia (BCP, n=12) or blood cardioplegia supplemented with glutamate and aspartate (26 mmol/L) (BCP+GA, n=10). Each patient had arterial and coronary sinus blood sampled, coronary sinus blood flow measured, and cardiac function evaluated by nuclear ventriculography.

Results: BCP+GA improved myocardial metabolic recovery and ventricular systolic function postoperatively. Both myocardial oxygen consumption (BCP+GA: 24.1+/-5.3; BCP: 10.4+/-2.2 mL/min, 3hr post-op, $p<.05$) and myocardial lactate flux (BCP+GA: 0.49+/-0.3; BCP: .08+/-.06 mL/min, 4hr post-op, $p<.05$) were improved. Left ventricular systolic function was better after BCP+GA because systolic blood pressures were higher at lower end systolic volume indices.

Conclusions: The addition of amino acid intermediates to blood cardioplegia improved myocardial metabolic recovery after elective CABG. These intermediates may reduce the morbidity and mortality of patients requiring urgent revascularization.

THE EFFECT OF AN APPLIED DIRECT CURRENT FIELD ON AXONAL COUNTS IN THE SPINAL CORD AFTER EXPERIMENTAL SPINAL CORD INJURY

Tat H. Wong*, Michael G. Fehlings, Charles H. Tator, Michael Tymianski
Division of Neurosurgery and Playfair Neuroscience Unit, Toronto Western Hospital

Experiments from our laboratory indicate that direct current (DC) stimulation promotes neurological recovery in adult rats with spinal cord injury (SCI). To examine the effect of DC stimulation on axonal counts at the injury site, we conducted a quantitative, morphometric analysis of axons at the site of SCI in rats treated with a DC field. Adult rats received either a 17g (n=10) or a 53g (n=15) clip compression injury of the cord at T1 and were treated with either a sham (0 μA) or a functioning (14 μA) DC stimulator for 8 weeks. After sacrifice and removal of the cord, serial 1 μM epon-embedded cross-sections of the injury site were stained with toluidine blue. The spinal cords from four normal rats were also examined. At 1000X magnification, the number, size, distance from the pia, and myelination index of axons intercepted by a series of 48 radial sample lines were analysed on line with a digitizing pad and computer. With an algorithm based on the line sampling theory, the total number of axons in the cord was estimated.

The mean number of axons in the normal spinal cord was 458,200.7 $\pm$ 49,571.6. There was a linear relationship (r=0.96) between the severity of SCI and the number of axons at the injury site. With the 17g injury, there was no significant difference in the number of axons between control (52,173.0 $\pm$ 23,206.1) and treated (55,095.8 $\pm$ 23,182.3) rats ($p>0.05$). However, at 53 g, treated rats (51,670.3 $\pm$ 8,289.3) had significantly more axons than controls (25,251.3 $\pm$ 8,449.3) ($p=0.017$). Both the 17g and 53g injuries caused preferential destruction of large calibre axons. Indeed, the mean axon diameter in normal cord was 1.94 $\pm$ 0.07 μM and in injured cord was 1.45 $\pm$ 0.10 μM ($p=0.0001$). Post hoc analysis (Tukey's HSD test) showed that the axon diameter of treated rats with 17g (1.46 $\pm$ 0.01 μM) and 53g (1.39 $\pm$ 0.01 μM) injuries was significantly greater than that of 17g (1.31 $\pm$ 0.02 μM) and 53g (1.17 $\pm$ 0.02 μM) controls. These data, for the first time, show that the application of a DC field increases the number of axons at the injury site and enhances the survival of large axons following SCI in the rat.

"NIBBLING VERSUS GORGING": METABOLIC EFFECTS OF PROLONGING THE RATE OF GLUCOSE INGESTION

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Past studies have focused attention on the benefits of "nibbling" versus "gorging". Taking smaller meals more frequently, as opposed to eating fewer larger meals was found to result in improved glucose tolerance in diabetic patients, and reduced serum cholesterol in normal volunteers and hyperlipidemic patients. In view of this we compared the metabolic effects, in nine healthy volunteers, of taking 50 g of glucose in 700 ml of water either as a bolus in 5-10 min, or sipped at an even rate over 3.5 h. Four hours after the start of the test, a 5 g intravenous glucose challenge (IVGTT) was administered. No difference was seen in the 4 h incremental blood glucose area despite a 40% reduction in insulin area ($p<0.05$) and an 80% reduction in C-peptide ($p<0.05$) after the sipping. Gastric inhibitory polypeptide, enteroglucagon, plasma glucagon, and urinary catecholamines were also lower after the sipping. After the IVGTT, a 30±10% more rapid disappearance of glucose was observed after the sipping as opposed to after the bolus. Although absolute levels of insulin and C-peptide were not different after the IVGTT, total branched chain amino acids were reduced after the sipping. In conclusion, these findings suggest that prolonging absorption may enhance insulin sensitivity and support the concept that prolonging absorption may be beneficial as a general therapeutic principle in the treatment of metabolic diseases.

MORPHOLOGICAL AND FUNCTIONAL MODELLING OF HUNTINGTON'S DISEASE AND ITS TREATMENT BY NEURAL GRAFTS IN RATS

Jennifer Schranz* and Michèle Pisa
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Injections of excitotoxins such as ibotenic acid in the rat's striatum simulate the pathology of Huntington's Disease, a disorder producing severe motor incapacitation. The effects of regional, ibotenate lesions of the rat's striatum on tongue reaching and forelimb reaching were examined. The study revealed a motor somatotopy in the lateral striatum: the dorsolateral region mainly mediates forelimb reaching and the ventrolateral region mainly mediates orofacial movements. A critical role of the lateral striatum in initiation, amplitude scaling and coordination of reaching movements was revealed. It has been reported that neural grafts in ibotenate lesioned striatum can promote recovery of some motoric alterations such as locomotor hyperactivity. Our next objective was to examine whether neural grafts can also promote recovery of reaching behaviors and whether homology of graft and host tissue is crucial. Bjorklund's procedure of cell suspension grafts was established in our laboratory. Rats were assigned to groups (n=10-13) for either vehicle control injections in the striatum, excitotoxin-induced striatal lesions followed by graft of striatal cells, or striatal lesions followed by graft of cortical cells. Cell suspensions were obtained from striatal or cortical primordium of Day 14-Day 15 rat embryos. Evidence of short-term graft survival has already been obtained. Behavioural testing and morphological study of long-term grafts will be started 4-5 months after grafting to maximize the opportunity for the grafts to re-establish functional connections.

ACID-INDUCED FUSION OF LIPOSOMES: STUDIES WITH 2,3-SECO-5α-CHOLESTAN-2,3-DIOIC ACID

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Negatively charged liposomes can be more efficiently internalized by mammalian cells through the endocytic-lysosomal fusion pathway if the liposome undergoes acid-induced fusion, resulting in the release of liposomal contents (such as drugs), into the cytoplasm after fusion of liposomal and endosomal membranes. We tested the hypothesis that the sterol derivative, 2,3-seco-5α-cholestan-2,3-dioic acid (SCD) would sensitize phosphatidylethanolamine (PE) vesicles to acid-induced fusion, using mixing of aqueous contents and lipid mixing assays to measure liposomal fusion of SCD- and non-SCD-containing vesicles. Mixing of aqueous contents of two populations of vesicles was measured by the decrease in fluorescence which occurred as the fluorophore-containing population was quenched by the quencher-containing population, as their aqueous contents mixed, subsequent to vesicle fusion. Lipid mixing was measured by the dilution of the resonance energy transfer between two fluorescent probes present in the lipid of one population of vesicles as its lipid mixed with the lipid of the unlabelled population of vesicles. Pure PE vesicles did not exhibit acid-induced fusion. PE vesicles with 2% (by weight) SCD did not show any fusion at pH 7.4, but substantial vesicle fusion was induced at pH 5.5-3.5, as measured by both assays. Vesicle leakage is neglible over the 7.4-4.25 pH range, but at lower pH or higher SCD concentrations, leakage occurs, and thus interferes with fusion measurements. The results suggest that SCD is potently fusogenic at low pH, when present at 2% by weight in PE vesicles. It is therefore potentially very useful for increasing the effectiveness of liposomal drug delivery.

ESTROGEN AND THE METABOLISM OF HIGH DENSITY LIPOPROTEIN IN RAT LIVER CELLS

Anthony V. Greco* and A. Angel
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Reduced levels of high density lipoprotein (HDL) are associated with increased risk of atherosclerosis. Evidence has accumulated that males and post-menopausal females have lower levels of HDL than pre-menopausal females. To study the effects of estrogen on the uptake and degradation of HDL by the liver, male rats were treated with pharmacological doses of 17-α ethinyl estradiol. Liver cells obtained by perfusion were incubated for 3 hours at 37° C with radioiodinated HDL. Total uptake of HDL by liver cells, represented by trichloroacetic acid (TCA) precipitable, cell associated radioactivity, was decreased by 50% with estradiol treatment, and was unaffected by ethylenediaminetetraacetic acid (EDTA), an inhibitor of the apoprotein (apo) B-E/E receptors of the liver. Non-specific binding in the presence of 40x excess unlabelled ligand was constant. HDL degradation, measured by the addition of cold 10% TCA to the incubation medium, followed by chloroform extraction of the TCA soluble supernatant, decreased by 44% and was unaffected by EDTA. In separate studies using female and male rats, consistently lower HDL uptake and degradation was observed for female rat liver cells. Inhibition of binding and degradation was observed with rat HDL, human HDL_3, but not with human low density lipoprotein (LDL).

These findings suggest that decreased binding and degradation of HDL by the liver are estrogen related and are major determinants of the higher levels of HDL observed in pre-menopausal females. Receptor-mediated binding of HDL to rat liver cells does not appear to be apo-E dependent. The higher levels of HDL due to sex hormone action at the liver may also play a part in determining the lower occurence of atherosclerosis in pre-menopausal females.

ADHERENCE OF VEROTOXIN PRODUCING *ESCHERICHIA COLI* SEROTYPE 0157:H7 TO EPITHELIAL CELLS IN VITRO

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Verotoxin producing *E. coli* of the serotype 0157:H7 have recently been associated with sporadic cases and outbreaks of hemorrhagic colitis and with the hemolytic uremic syndrome. In addition to toxin production, adherence of pathogens to mucosal surfaces is an important step in the pathogenesis of many infectious diseases. *E. coli* 0157:H7 adhere to epithelial cells in tissue culture and to the intestinal surface in orally infected rabbits. To determine if *E. coli* 0157:H7 adhere to post-natal human epithelial cells in vitro, we isolated human buccal epithelial cells from adult volunteers and isolated enterocytes from the ileum and colonocytes from the colon of human surgical resection specimens. Ileal brush borders and colonocytes were also prepared from rabbits. Five *E. coli* 0157:H7 strains, an *E. coli* strain previously shown to adhere to human enterocytes (positive control), and a human fecal commensal *E. coli* (negative control) were incubated with epithelial cells and brush borders under conditions previously used to demonstrate adherence of other pathogenic *E. coli*. Adherence of bacteria to isolated epithelial cells and brush borders was determined using both phase contrast microscopy and a solid phase microtiter assay. Four non-piliated *E. coli* 0157:H7 strains did not adhere to buccal cells, ileal enterocytes, colonocytes or rabbit ileal brush border membranes. In contrast, the one piliated *E. coli* 0157:H7 strain adhered to each type of epithelial cell preparation. Saturable binding of the piliated strain to rabbit ileal brush borders was optimized with respect to pH and temperature. We conclude that cell surface antigens, such as pili, may mediate attachment of these organisms to mucosal surfaces. However, most *E. coli* 0157:H7 strains do not attach to human epithelial cells under in vitro conditions appropriate for binding of other pathogenic *E. coli*.

PROTECTION OF NEWBORN HEARTS: THE EFFECT OF EXTRACELLULAR CALCIUM ON THE DEVELOPMENT OF IRREVERSIBLE ISCHEMIC INJURY

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Previous work in this laboratory has demonstrated a greater relative vulnerability of the newborn myocardium to damage induced by global ischemia when compared to adult myocardium as measured by a much shorter time to both the onset of ischemic contracture[TIC(o)] and peak ischemic contracture. Time to ischemic contracture (TIC) is an accepted indicator of irreversible ischemic damage. In adults, the development of ischemic rigor complexes and TIC(o) are calcium-insensitive; the availability of calcium may only influence the magnitude of the final developed pressure. The newborn cardiomyocyte is felt to be more sensitive to extracellular calcium than adults. Alterations in extracellular calcium, therefore, may influence ischemic myocardial contracture in neonates to an extent not observed in adults and may allow an explanation for the increased sensitivity of newborn hearts to ischemia. To test this hypothesis, 3 day old male piglets (n=20) were used. The excised, potassium-arrested hearts of these piglets were perfused for two minutes under conditions of normothermia (38° C) with substrate-free Krebs-Henseleit (SFKH) solution containing one of three different calcium concentrations: 1) no calcium (n=9) 2) normal calcium (n=9) 3) high calcium (n=2). Perfusion was then halted and the hearts were transferred to normothermic SFKH baths containing calcium concentrations identical to those used in the perfusate; the time to ischemic contracture (TIC) was noted as a 2 mm Hg rise in pressure recordings from a compliant latex rubber balloon inserted into the left ventricle. The results are as follows:

Group	SFKH [Ca^{2+}] (mmol/L)	TIC(o) (min)	TIC(p) (min)	Peak Ischemic Pressure(mmHg)	2 min Effluent [Ca^{2+}](mmol/L)
1	0.13	45.1±1.3	18.2±1.0	42.8±4.0†	0.12±.01†
2(control)	2.23	47.4±2.0	17.1±1.5	58.1±2.8	1.92±.01
3	4.44	40.0±2.0	17.5±0.5	63.5±18.5	3.78±.06†

†=significant ($p<.05$) from control (by ANOVA/TUKEY); TIC(p)=peak TIC - TIC(o)

We can conclude that for newborn myocardium, the availability of extracellular calcium does not significantly ($p>.05$) influence the onset and duration of ischemic contracture, but may play a role in determining the peak pressure generated. These results parallel closely the findings observed for the adult myocardium, and thus suggest that the observed differences between neonatal and adult vulnerability to ischemic myocardial damage cannot be explained primarily by differences in sensitivity to extracellular calcium.

LV DIASTOLIC FUNCTION IN SYSTEMIC LUPUS ERYTHEMATOSUS

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We found acute cardiogenic pulmonary edema in association with impaired diastolic normal LV systolic function to complicate the course of some patients with active systemic lupus erythematosis (SLE). The current study was performed in an attempt to determine 1) the prevalence of IDF in a cross-sectional population of SLE patients and 2) whether degree of IDF correlates with clinical SLE disease activity. Isovolumic relaxation time (IVRT) and the following pulsed Doppler indices of mitral inflow: early (E) and late (A) velocity peaks, their ratio (E/A) and mitral pressure halftime (PHT) were measured in 35 SLE pts (age=41±16yrs) and in 30 age matched normals (N). SLE pts were stratified to active disease (AD) and inactive disease (ID) according to the previously validated Lupus activity criteria count of ≥2 and <2 respectively.

		HR	IVRT	E	A	E/A	PHT
N	(30)	66	74	0.83	0.59	1.47	65
SLE	(35)	73*	89*	0.74*	0.55	1.47	72*
SLE-AD	(14)	70	104*	0.69*	0.65	1.18*	74*
SLE-ID	(21)	75*	80*	0.77	0.48	1.65	71

(p≤0.05 compared to N; IVRT, PHT-mSec; E, A-m/s)

IDF with prolonged IVRT (>100mSec) as its most sensitive indicator was common in SLE, seen in 9/14 (64%) AD pts of which 2 had heart failure, and in 3/21 (14%) ID pts. In addition, the longer IVRT, lower E point and lower E/A ratios in AD suggest a relatively greater degree of IDF in SLE pts with AD as compared to ID. All pts were normotensive at time of study and history of hypertension was similar in AD and ID pts at <20%. Echocardiographic measurements of LV size, systolic function and wall thickness were also similar in both groups. One AD pt had abnormal systolic function by 2D echo.

Conclusions: 1) IDF occurs commonly in SLE and 2) although usually subclinical, IDF is more frequent and more pronounced in active SLE where it is occasionally associated with development of clinical heart failure. These findings suggest that functional myocardial involvement in SLE is of a greater degree than previously suspected and may be related to disease activity.

A VECTOR COMPUTER MODEL OF RENAL PAH TRANSPORT

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A vector computer (large scale computational) study of renal multiple indicator dilution (MID) was carried out. MID is a bolus-injection, single-pass tracer method that resolves the kinetics of glomerular and post-glomerular transport in vivo. The model was developed in mathematical form. Epithelial cells were arranged in a layer between a vascular-interstitial space and a lumen or urine-forming space. Convection occurs in the vascular space and may occur, modeled by an effective sequestration rate constant, in the lumen space. Transport of tracer takes place between the cell and the vascular-interstitial space and between the cell and the lumen space. Tracer molecules may be degraded or irreversibly sequestered within the cells. Tracer exchange across the capillary wall is flow-limited. Capillary transit times were distributed heterogeneously. Integration over single exchange unit behavior connected the cellular level to the whole-organ level. The model's natural vector structure was used to implement it as a parallel computational process. The mass balance and kinetic equations for the indicator dilution properties were solved and applied to empirical data in the kinetics of para-aminohippurate (PAH) transport in dog kidney. PAH is the prototypic organic anion used to study anionic transport across the renal proximal tubule. This vector computer model has been applied to a series of over 70 experimental runs in which the MID method was applied to tracer-level PAH secretion in the renal cortex proximal tubule of anesthetized mongrel dogs (M. Silverman, C. Whiteside, empirical studies). Pulse injections were made into the renal artery with a bolus containing radioactively labeled albumin (ALB) (vascular reference), creatinine (CR) (extracellular reference) and PAH. Timed serial samples were drawn simultaneously from the renal vein and ureters. A vector algorithm was applied to find the best fit to the data, with a fitting criteria of least squares. Average unidirectional steady-state tracer PAH coefficients in the absence of background PAH were quantified. The ratio of tracer uptake to outgoing tracer permeability coefficients localizes active uptake and net secretion of PAH under in vivo conditions.

NALBUPHINE AS AN ADJUNCT TO MASK ANAESTHESIA WITH ISOFLURANE

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Isoflurane (Forane) is a volatile anaesthetic gas with many desirable properties. When given by mask, however, isoflurane frequently induces troublesome respiratory phenomena such as coughing and laryngospasm. The hypothesis of the study was that a small intravenous dose of nalbuphine (Nubain), a narcotic agonist-antagonist, three minutes prior to anaesthetic induction, would reduce the incidence of these reflexes. In this prospective, randomized and double blind study, ninety healthy subjects were given one of three mask anaesthetics — halothane alone, isoflurane alone and isoflurane with nalbuphine. A variety of data was gathered during the period of anaesthetic induction, including the number and type of respiratory reflexes and oxygen saturation. The addition of nalbuphine to isoflurane significantly lowered the incidence of excitatory respiratory reflexes. Isoflurane anaesthesia (with or without nalbuphine) was associated with a significantly increased number of desaturations (defined as an $Sa0_2$ of less than 90%) but these episodes were brief and without clinical sequelae. Arterialized venous blood gases showed no difference between groups in mean pCO_2 following surgical stimulation. We concluded that the addition of nalbuphine to isoflurane blunts excitatory respiratory phenomena without significantly increasing respiratory depression.

REENTRY AND DEVELOPMENT IN SELECTIONAL BRAINS: MEMBRANE EQUATIONS AND SIMULATION

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A computer simulation was devised to study the effects of long-term synaptic facilitation and phasic reentry on systems of neuronal groups. Each neuronal group recognized and responded with specific levels of activity to sequences of input stimuli. Included in the simulation were patterns of intergroup connectivity, synaptic weight terms, parallel processing, and feedforward and feedback effects. Analysis of activation responses in the repertoire suggest several key factors modulating development in selectional brains.

THE DIFFERENTIAL ADHESION KINETICS OF MITRAL VALVE INTERSTITIAL CELLS AND AORTIC WALL CELLS

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Since very little is known about the function of mitral valve interstitial cells (MVIC), we have developed a cell culture system to study them. MVIC were harvested from explants of the anterior leaflet of the porcine mitral valve. After 20 passages some cultures contained elongated (EL) cells with prominent stress fibres, while others showed predominantly cuboidal (CB) cells with prominent endoplasmic reticulum and Golgi. As part of our characterization of these cells, the parameter of cell adhesion was assessed and compared to that of porcine aortic endothelial and smooth muscle cells. The adhesion assay involved plating freshly trypsinized cells on tissue culture dishes (an excellent substratum) and on petri dishes (a poor substratum for adhesion of cells), applying reproducible agitation to the dishes at given time points following plating, and counting the adherent cells with a Coulter counter. Our data show that the EL cells adhered better than the CB cells. On petri dishes both cell types did not show any appreciable adherence up to 24 hours after plating. At 24 hours 52.8 $\pm$ 1.8% (mean $\pm$ standard error in the mean) of the EL cells adhered per dish, while only 37.6 $\pm$ 7.2% of the CB cells adhered. On tissue culture, after 1 hour 78.6% $\pm$ 2.0% of the EL cells had adhered, while only 34.2% $\pm$ 8.7% of the CB cells adhered per dish. At 24 hours 85.4% $\pm$ 3.1% of the EL cells and 75.7% $\pm$ 4.8% of the CB cells had adhered. Our data also showed that both types of interstitial cells adhered more slowly than did aortic endothelial and smooth muscle cells. This was most evident on petri dishes in which, at 1 hour, no adherence was detectable in EL and CB, while 13.7% $\pm$ 5.2% of the smooth muscle cells and 46.1% $\pm$ 11.4% of the endothelial cells adhered per dish. These results are the first to suggest that the MVIC display heterogeneity and may represent two distinct cell types or two different phenotypic states of the same cell type.

PHOTOAFFINITY LABELING OF OPIOID RECEPTOR OF RAT BRAIN MEMBRANES WITH ^{125}I(D-Ala^2, p-N$_3$-Phe^4-Met^5) ENKEPHALIN

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A photoreactive (D-Ala^2, p-N$_3$-Phe^4-Met^5) enkephalin derivative was prepared, iodinated with carrier free ^{125}I and then purified by high performance liquid chromatography. The purified radioactive photoprobe was monoiodinated at the amino terminal tyrosine residue. This radioactive photoprobe was used to photo-affinity label membranes prepared from the rat brain (minus cerebellum) and the spinal cord. The photolabeled membranes were analyzed by sodium dodecyl sulfate gel electrophoresis. A 46,000-daltons protein was specifically photolabeled in these membrane preparations. The photolabeling of this protein was inhibited by peptides related to enkephalin but not by unrelated substance P or gastrin tetra-peptide. A concentration dependent inhibition of the photolabeling of the 46,000-daltons protein was observed in the presence of competing ligands specific for the μ-, δ- and κ-opioid receptors. These data demonstrate that the radioactive photoprobe labels the μ-, δ- and κ-opioid receptors. Although there is no evidence available to show that the 46,000-daltons protein is identical in all the cases, our data strongly suggest that it is a binding protein common to all of the opioid receptor subtypes.

FINITE ELEMENT ANALYSIS OF PULSATILE BLOOD FLOW THROUGH A TUBE WITH AXIALLY-SYMMETRIC STENOSIS

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There is considerable evidence that hydrodynamic factors can play a significant role in the development and progression of atherosclerosis. The present study was undertaken to investigate numerically the mechanics of pulsatile flow through a straight tube with minor stenosis.

The flow was described by the Navier-Stokes equations and the continuity equation. The numerical method used was based on Galerkin's finite element approach with a 'mixed-interpolation' formulation. The resulting set of non-linear simultaneous equations was solved iteratively by Newton-Raphson method. Time-integration was performed by using finite difference method. Euler Backward difference formula was found to be more stable but less accurate and the converse was true for Crank-Nicolson scheme. The numerical model was verified by comparing the numerical results with those predicted by Womersley's solution. The accuracy of the numerical model was very good: <3% error when 12 time steps were used.

For flow through a stenosed tube, the Reynolds no. at the inlet ranged from 125 in diastole to 750 in systole. There was a localized vortex just downstream of the stenosis and during the deceleration phase, the flow became less stable and the vortex enlarged and grew towards the outlet.

In conclusion, preliminary studies showed that this finite element procedure could predict pulsatile blood flow satisfactorily.

5-FLUOROURACIL INFUSIONS AND FRACTIONATED RADIATION: COMBINED EFFECTS ON A MURINE SQUAMOUS CELL CARCINOMA

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Recent clinical trials combining 5-Fluorouracil (5FU) infusions and fractionated radiation for treatment of squamous cell carcinomas show promise of improved local control and/or increased therapeutic ratio. The present investigation was undertaken to examine experimentally the effects of combining radiation and 5FU, with emphasis on 5FU infusions. A transplantable murine tumor of squamous cell origin, SCC VII/To, was grown intramuscularly in the hind legs of C3H mice. Tumors of 0.3g were irradiated with single or fractionated local doses of 100 kVp X-rays, 11 Gy per min, alone or in combination with i.p. bolus injections or 4-14 day infusions of 5FU, using subcutaneously implanted mini-osmotic pumps. Studies done with radiation alone indicated that regrowth delay increased with total dose but this increase was less for fractionated than single doses. The effects of 5FU as a single agent were measured using either i.p. injections, 4, 7 or 14 day infusions. Tumor response to i.p. injections or 4 day infusions were not significantly different. The LD_{50} for i.p. bolus injections was similar to that for a 7 day infusion (230-270 mg/kg). For total doses up to 200 mg/kg 5FU, 14 day infusions were least effective, 4 day infusions were intermediate and 7 day infusions were most effective. Above 280 mg/kg, 14 day infusions became most effective. When a constant 7 day infusion of 5FU (130 mg/kg) was combined with increasing total radiation doses (single or 5 fractions), the regrowth delay enhancement was additive, diminishing slightly at higher radiation doses. When a constant fractionated dose of 5 Gy per day for 5 days was combined with increasing total doses of 5FU (i.p. or 4, 7, 14 day infusions) all schedules showed an enhanced regrowth delay, consistent with an additive interaction of the agents. Administering a total dose (i.p. or 7 day infusion) of 5FU (130 mg/kg) starting 2 days before, during, or immediately after a fractionation schedule of 5 Gy per day for 5 days gave the same regrowth delay, indicating no effect of drug scheduling. In conclusion, the above data indicate that 1) 5FU infusions (>4 days) are more effective than bolus drug administration in inhibiting SCC VII/To tumor growth and 2) the results obtained by combining 5FU and radiation are consistent with an additive interaction of the two agents with no dependence on the sequencing of the two agents.

RADIOIMMUNOASSAY (RIA) FOR THE DETECTION OF 2G3 ANTIGEN LEVELS IN OVARIAN CANCER PATIENTS

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Recently, ^{125}I-labelled 2G3 monoclonal antibody has been used for the treatment of ovarian cancer. This antibody (Ab) localizes to 2G3 Antigen (Ag) presented on the surface of the tumour cells, emits its beta energy, and thus, destroys the malignant cells. A simple assay was devised to monitor the therapy of patients undergoing immunotherapy. With the use of 2G3 Ab-coated immunobeads, a sandwich RIA was developed to detect 2G3 Ag levels present in a lysate obtained from MCF/7 cells (breast tumour cells). Experimental conditions such as choice of non-specific blocking agent, amount of 2G3 Ab-coated beads, amount of ^{125}I-2G3 Ab tracer, etc., were optimized to obtain the most sensitive test. The assay was then performed on ascites fluid obtained from ovarian cancer patients. Two of the patients tested had not been previously screened for the presence of 2G3 Ag, while the third patient was known to be positive for 2G3 Ag. Although the samples from the patients whose 2G3 Ag status was unknown demonstrated saturation binding effects, all the samples tested revealed that the RIA was sensitive in detecting varying levels of 2G3 Ag. A linear relationship was observed between the amount of 2G3 Ag present in the ascites fluid and the amount of tracer bound. These results indicate that the levels of antigen present in the ascites can be determined from a comparison with the standardized control antigen. Thus, the sandwich RIA developed may be used to monitor circulating levels of 2G3 Ag present in ovarian cancer patients receiving immunotherapy.

EVALUATION OF PARAMETERS FOR DOSE-RESPONSE RELATIONSHIPS: THE HILL EQUATION

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A new graphical method (SLL — Slope of Log Log plot) was devised to evaluate parameters of dose-response relationships (DRR) under low dose conditions. DRR often follow Hill equation $y=Ac^N/(B^N+c^N)$ where y is the response, and c the concentration. The parameters are A (the maximum response), B (an analogue of ED50) and N (the Hill coefficient, a measure of steepness). SLL utilizes a feature of the Hill equation: in the plot (log y vs. log c), the slope varies according to $Slope=N(1-y/A)$. Therefore, N can be evaluated as the initial slope measured at low c, A from response and slopes obtained at higher c (but not necessarily at high c), and B from the Hill equation, A and N. It is important that the method can also be applied when all observed responses are far from their maximum. The effectiveness of SLL was tested using computer simulated experiments with various ranges of errors and c. The precisions and accuracies of the calculated parameters were compared with those obtained by weighted non-linear least squares (LS). Results of SLL are almost as good as those of the idealized LS. For a maximum y of 0.4, SLL can tolerate an experimental error of 5%, while LS permits 5.5%. However, LS requires good initial estimates for the parameters, and this poses a difficult problem. The new SLL can readily provide these estimates. In addition, SLL is about 10 to 20 times faster than LS. The new procedure also has useful graphical features which permit analytical insights.

CONDITIONED SENSITIZATION OF THE IMMUNE RESPONSE TO REPEATED ANTIGENIC PRESENTATION OF OXAZOLONE

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If an animal's response to a stimulus is partially dependent on the environment in which the stimulus has been presented in the past, then the response is said to be conditioned or learned. Two experiments demonstrate an environmental specificity to the hypersensitive response to oxazolone in CBA mice, and suggest that learning accounts for part of the hypersensitivity or tolerance shown by the immune system in response to antigenic stimulation. Mice were fed the antigen oxazolone as a 10 mg dose by intubation. Six days later the animals were challenged with antigen by painting 20 μl of 1% oxazolone solution on the ear. The contact sensitivity evoked was measured 24 hrs later as the ear swelling response. Each feeding and painting of antigen were paired with a novel environment (specific room and handling procedures). A steady hypersensitive response developed in the conditioned groups. On the last oxazolone presentation some of the animals were fed and painted in a second novel environment. These animals, presented with only the unconditioned stimulus on the last pairing, showed a decreased ear swelling response. This demonstrated an environmental specificity of the immune response to repeated antigenic presentation. We suggest that stimulation of the immune system by oxazolone primarily activates an afferent arm of the nervous system, and thus provides an unconditioned stimulus for classical conditioning.

ANTICIPATED AND EXPERIENCED STRESSES OF STUDENTS ENTERING THE CLINICAL CLERKSHIP YEAR OF STUDY

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Previous research has suggested that some students both tolerate stress well and even thrive in an environment that they perceive to be stressful. The study reported here analyzed the anticipated and experienced stresses of students entering the clinical clerkship year. Students who elected to take Surgery or Medicine (N=80) as their first rotation and a control group of students in other rotations (N=20), completed a pre- (on first day of clerkship) and post- (8 weeks later) questionnaire. Twenty stress-retaled items were identified and rated on a scale of 1 to 5. Responses were analyzed in relation to demographic variables. Significant differences were observed for all students on the pre- and post-questionnaires in regard to 13 of the 20 stress items ($p<0.05$). In most cases, the degree of stress experienced was lower than had been anticipated, with the exception of the items dealing with amount of time available for study, concern about learning and impact on social life. Differences were also observed for sex, career choice, age and marital status ($p<0.05$). These findings suggest that much can be done to alleviate student concerns prior to entry into the clinical clerkship. Clerkship Directors need to address the issue of availability of time to study in the clinical clerkship.

A NON-INVASIVE MEASUREMENT SYSTEM FOR THE PREDICTION OF THE LUMBOSACRAL ANGLE

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Through the development of a non-invasive measurement system a method of predicting the locations of vertebral body centroids allowed for the prediction of the lumbosacral angle (LS). Data was collected from 12 adolescent lumbar spines with applied radio-opaque skin markers placed over lumbar spinous processes and radiographed in the lateral plane. The procedure involved developing a lumbar mapping function based on a cardinal spline function (Bethune et al., 1986) derived from the differences between skin curve and vertebral body centroid curve splining functions. Ability to predict lumbar centroid positions within an averaged error of 2 mm. allowed for the use of the predicted splined centroid curve, its associated lumbar centroid slopes and arctan differences of centroids, to calculate reciprocal angles between vertebral bodies. These calculated reciprocal angles were considered as being implicitly related to the orientation of sacral surface in space. Prediction of the LS angle was considered by linear regression using L2L3, L3L4, L4L5 reciprocal angles, the arctan L5 (representing L5 orientation to the horizontal), and subject age. The predictes LS angle was compared with manual measures of this value. The results showed a statistically significant ($p>.0001$) ability to predict LS with a R^2 or 0.94.

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THE ROLE OF EXTRACELLULAR CALCIUM IN ISCHEMIA-REPERFUSION INJURY

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Ischemia-reperfusion injury to skeletal muscle, following an acute arterial occlusion is a significant cause of morbidity and mortality. The purpose of this study is to examine the role of extracellular calcium in the production of cellular necrosis following a prolonged period of normothermic ischemia. Bilateral canine gracilis muscles were made ischemic for 4.5 to 5 hrs. The control muscle was perfused for 30 min with an oxygenated solution (Ca^{++} .11mM) containing S.O.D. the normal perfusion restored. Necrosis was determined using nitroblue tetrazolium staining. Total muscle Ca^{++} was measured by atomic absorption spectrometry. Pre and post ischemia muscle Ca^{++} levels were similar (2.8 ± 0.4 vs 3.0 ± 0.8 nmole/mg protein, $n=6$). After 30 min of reperfusion the treated muscle Ca^{++} was 1.7 ± 0.6 compared to control levels of 9.2 ± 0.9 nmole/mg protein, $p<0.001$). Total tissue calcium returned to normal at 60 min in viable muscle, but continued to accumulate in necrotic tissue. However, the delay in initial muscle Ca^{++} influx was not associated with the increased overall salvage of muscle (76 ± 8.6 vs 75 ± 8.0% necrosis, p=NS). In conclusion we could not demonstrate a protective effect of reduced extracellular Ca^{++} during early reperfusion. In fact it negated our previously demonstrated beneficial effects of free radical scavengers. Therefore manipulation of extracellular Ca^{++} concentration may not be a suitable therapeutic intervention for reducing ischemia-reperfusion injury to skeletal muscle.

ACUTE EVOLVING MYOCARDIAL INFARCTION: AN EXPERIMENTAL COMPARISON OF MEDICAL VS. SURGICAL REPERFUSION

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Patients with an acute myocardial infarction require urgent reperfusion to limit the infarct size. However, percutaneous coronary angioplasty usually produces a substantial infarct. Modifying the conditions of reperfusion may limit the myocardial infarction. We evaluated three alternative methods of reperfusion after 2 hours of left anterior descending (LAD) occlusion in a canine model. Reperfusion was established by: 1) release of the occlusion (angioplasty, n=7), 2) release of the occlusion during cardioplegia arrest on cardiopulmonary bypass (to simulate an urgent coronary bypass operation, n=6) or 3) release of the occlusion during veno-arterial extracorporeal membrane oxygenator (ECMO to reduce the energy demands of the heart during angioplasty, n=7). After 4 hours of reperfusion, the extent of myocardial infarction within the area at risk (AI/AR) was evaluated by infusing Evans blue into the aortic root (with the LAD occluded) and tetrazolium into the area at risk. The area at risk was similar in each group. Angioplasty resulted in an infarct of 28+/-5% of the AR. Surgical reperfusion resulted in an infarction of 6+/-3% of the AR. Angioplasty during ECMO produced an infarction of 13+/-8% of the AR. (The groups were different, $p<0.05$ by analysis of variance). Thallium 201 scans performed before and 2 hours after reperfusion revealed better preservation by surgical than medical techniques. Myocardial biopsies showed better preservation of adenosine triphosphate concentrations with surgical reperfusion. Modifying the conditions of reperfusion minimized the infarct size after angioplasty in a canine model of an acute myocardial infarction.Either coronary bypass surgery or ECMO may provide better results than angioplasty.

IMMUNOLOGICAL BASIS OF ROSETTE FORMATION

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Numerous investigators have reported that mouse thymocytes preferentially form rosettes with syngeneic compared to allogeneic erythrocytes. We further investigated the immunological basis of this phenomenon. Thymocytes and erythrocytes from different mouse strains were obtained in a sterile manner, washed, and incubated together at 4°C for an hour. The percentage of rosette formation, for each thymocyte-erythrocyte combination, was obtained by determining the ratio of thymocytes binding 4 or more erythrocytes to total number of thymocytes. Aggregates of thymocytes were excluded from the count. Combinations with full major histocompatibility complex (MHC) identity showed a higher frequency of rosette formation than those with no MHC identity. When the indolizidine alkaloid, swainsonine (SW), was included in the assay, the frequency of rosettes in MHC identical combinations was reduced to that seen in MHC non-identical combinations while the latter were unaffected. Moreover, anti-MHC monoclonal antibodies were able to block rosette formation in MHC identical combinations, but not in MHC non-identical combinations. Combinations with only partial identity at MHC behaved like those with no MHC identity. Hence, absolute identity at MHC is required for optimum rosette formation, and that partial identity at MHC, either by sharing or by overlapping of MHC determinants, is not sufficient to elicit the maximal rosette formation. Use of appropriate monoclonal antibodies suggests that rosette formation does not involve the T-cell receptor, but instead involves molecule(s) involved in general cell adhesion. Thus, our results imply that cell adhesion phenomena involve and are restricted by products of the MHC.

CHANGES IN ARTERIAL PRESSURE AND HEART RATE ELICITED BY MICROSTIMULATION OF CELL BODIES IN THE HYPOTHALAMUS OF ANESTHETIZED RATS

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Electrical stimulation of discrete hypothalamic sites of anesthetized animals elicits visceral responses including changes in arterial pressure (AP) and heart rate (HR). As electrical stimulation excites neural tissue non-selectively, these cardiovascular responses could be due to the excitation of fibers of passage as well as the cell bodies of interest. A systematic exploration of the hypothalamus of urethane anesthetized (1.4 g/kg i.p.), paralyzed and artificially ventilated male Wistar rats was made with pressure microinjections of an amino acid that selectively excites neural somata. AP and HR were recorded continuously. Amounts from 5-50 nl of a 0.15 M solution of dl-homocysteate (DLH; pH 7.4) was delivered through stereotaxically positioned glass micropipettes. Injection sites were histologically verified. A total of 418 sites were stimulated in 46 rats. In 271 sites (65%) depressor responses and in 77 sites (18%) pressor responses were elicited, ranging from -5 to -32 mmHg and +5 to +47 mmHg, respectively. 70 sites (17%) were not responsive. Depressor effects had a shorter latency (85% started within 5 s) than pressor effects (42% started within 5 s). Analysis of the anatomical distribution of responsive sites showed that in all hypothalamic subdivisions depressor responses predominated, except in the paraventricular nucleus. Increases in HR predominated in nuclei located near the 3rd ventricle, whereas decreases in HR were obtained from lateral and caudal sites. These results suggest that the classical division of the hypothalamus into a rostral depressor and a caudal pressor area is probably due to the excitation of fibers of passage.

NOCTURNAL VENTILATORY SUPPORT AT HOME

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Effective nocturnal mechanical ventilatory support in patients with respiratory failure can stabilize the clinical course of their condition and disease, improve their daytime arterial blood gases and their daytime level of functioning. Such patients may be managed in the community following stabilization and training in the hospital. Between 1985 and 1987, 15 patients (8 male, 7 female) aged (mean ± SD) 50 ± 11 years have been maintained at home on nocturnal ventilation. Two have C.O.P.D., 13 have restrictive lung disease. Ventilation was commenced electively in 12 patients, by positive pressure in 10 patients (8 tracheostomy and 2 nasal mask) and by negative pressure in 5 patients. In 18 months prior to ventilation, patients spent 45 ± 103 days in hospital (ICU 18 ± 23 days). For 18 months post ventilation, this time was reduced to 25 ± 50 days (ICU 3 ± 6 days). One patient with C.O.P.D. died at home. Six minute walk tests improved from 324 ± 109 metres to 452 ± 187 metres. Arterial blood gases at room air improved significantly: (pre $PaCO_2$ 60 ± 7 mmHg, PaO_2 42 ± 11 mmHg, O_2SAT 80 ± 6 %, post $PaCO_2$ 46 ± 5, PaO_2 69 ± 11, O_2*SAT* *92* ± 3). Support required for 13 patients (in hours per week) is; nursing 0.5 ± 0.6; occupational therapy 0.2 ± 0.5; physiotherapy 0.1 ± 0.4; respiratory therapy 0.3 ± 0.5; social services 0.1 ± 0.3; homemaker 1.8 ± 2.9. Nine patients are on Home Care (at no direct patient cost). We conclude that nocturnal home ventilation is an effective, safe and inexpensive approach to the management of patients with stable respiratory failure.

ADEQUACY OF PAP SMEAR SCREENING LOOKOUT ZONE

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The evidence of cancer of the cervix is approximately four times greater for Canadian Inuit and Indian women than for non-native women. Screening programs are of great importance in these groups. The objective of this study was to assess the adequacy of the cervical cytology (Pap Smear) screening program in Native women in the Sioux Lookout Zone of Northwestern Ontario for the time period between January 1, 1977 to December 31, 1986. The medical charts of 1000 randomly selected females between the ages of 20 to 75 years who were living continuously on reserve were reviewed. The following information was collected: age, gravida, age of first pregnancy and whether individuals had pap smears. If yes, then dates of smears, reasons for smears, results of smears and type of followup received in case of abnormal smear were described. It was found that women in the 20 to 35 years category received adequate pap smear screening according to Canadian standards, i.e. once a year. In fact there was a degree of overtesting for some of these women. The majority of the pap smears were performed for pregnancy purposes (pre or postnatal or birth control) as opposed to routine "Well Woman Check" screening. As women progressed in age above 35 years, from 35 to 60, the frequency for pap smears decreased in a linear manner with a great decline in the over 45 category, the menopausal period. Of those receiving pap smears in older women the reasons were primarily for symptomatic complaints.

PREVALENCE OF *CHLAMYDIA TRACHOMATIS* IN ADOLESCENT FEMALES

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We retrospectively studied the prevalence of genital chlamydial infection in sexually-active females twelve to twenty years old. Subjects presented to an adolescent medical clinic at a downtown paediatric hospital from 1983 to 1986. Two markers of acute infection were followed: (1) chlamydial isolation rates from genital tract swabs, and (2) the presence of high titre (1:64) anti-chlamydial antibody in serum. Chlamydial isolation rates increased 2.8 fold from 5.5% in 1983 to 17.6% in 1986. Over the same period the proportion of adolescent females with high antibody titres increased three fold. Agreement between these two independent markers of acute infection is consistent with increasing prevalence. Chlamydial isolation rates also increased five times faster than isolation rates for *Neisseria gonorrheae* from 1983 to 1986. These findings suggest chlamydial infection must receive greater consideration in the differential diagnosis of adolescent genital tract infection.

ACETYLCHOLINESTERASE AND BUTYLCHOLINESTERASE ACTIVITY OF NEURITIC PLAQUES IN ALZHEIMER'S DISEASE AND THEIR INHIBITION BY SELECTIVE ENZYME INHIBITORS

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Alzheimer's disease is the most prevalent form of dementing illness, and is distinguished neuropathologically by the presence of neuritic plaques and neurofibrillary tangles found predominantly in the cerebral cortex. The histochemical distribution of cholinesterase (labeled by a modification of the Karnovsky-Roots technique with cobalt chloride-diaminobenzidine intensification) was investigated in brains from patients who died with Alzheimer's disease and in brains from control patients. In addition, the response of cholinesterase staining to specific enzyme inhibitors was examined. In the neocortex of control brains most of the cholinesterase activity was located in axons belonging to subcortical neurons of the cholinergic systems and in noncholinergic cortical neurons. In contrast, in the neocortex of Alzheimer's brains axons and cell bodies displaying cholinesterase activity were found to be severely depleted. Nevertheless the neocortex of Alzheimer's brain exhibited considerable cholinesterase activity which was localized largely to neuritic plaques. The acetylcholinesterase labeling of normal axons and cell bodies in control brains and the acetylcholinesterase labeling of neuritic plaques in Alzheimer's brains could be completely inhibited by low concentrations (10^{-6}M) of the specific acetylcholinesterase inhibitor BW284C51. The neocortex of control brains exhibited virtually no butylcholinesterase activity of axons or cell bodies. Nevertheless, in the neocortex of Alzheimer's brains considerable butylcholinesterase activity was localized to neuritic plaques. This butylcholinesterase activity could be completely inhibited by preincubation with low concentrations (10^{-5}M) of a specific butylcholinesterase inhibitor ISO-OMPA. In patients with Alzheimer's disease, cholinesterase inhibitors therefore appear to have a major and widespread effect directly upon the enzymatic activity of neuritic plaques. Therefore it is conceivable that the clinical effects of memory improvement that anticholinesterase agents produce in Alzheimer's disease may be based on a mechanism that is quite distinct from the mechanism of action (potentiation of cholinergic transmission at the synapse by inhibition of the degradation of acetylcholine) that is proposed as the basis of the effect of cholinesterase inhibitors in the normal brain.

THE BRINE SHRIMP *ARTEMIA* AS A BIOLOGICAL ASSAY FOR ORGANIC AND INORGANIC MERCURY

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Mercury compounds are known to cause both developmental and physiological abnormalities in many animals including man. It is also recognized that organic mercury compounds are potentially much more harmful than inorganic mercuries. It was the purpose of this study to set up a biological assay for mercury compounds that would be both statistically significant and sensitive to differing mercury compounds and minute concentrations. This assay could then be readily used to determine the safety of various water sources to humans. For this purpose, the brine shrimp, *Artemia,* was utilized. The compounds $HgCl_2$, CH_3HgCl, $(CH_3)_2Hg$, CH_3CH_2HgCl, and $C_6H_{12}HgCl$ in the concentrations 10μm, 5μm, 1μm, and .1μm were introduced into the environment of the developing brine shrimp. Two hundred brine shrimp were subjected to each treatment. It was found that organic mercuries had greater adverse effects than the inorganic compound and different concentrations of each compound produced different results. It was concluded that *Artemia* could indeed be utilised as a biological assay for mercuric compounds as it fulfilled the requirements outlined earlier.

MORPHOLOGICAL AND PHYSIOLOGICAL STUDIES OF LONG-TERM FACILITATION (LTF) IN CRAYFISH'S NEUROMUSCULAR JUNCTION (NMJ)

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One of the many challenges in Neurobiology is the understanding of the cellular and molecular basis of learning. The most prevalent theory of learning proposes that this process is dependent on strengthening of certain synaptic connections between nerve cells. The strengthening can be enhanced by introducing changes in activity that alter structural and functional properties of pre- or post-synaptic components of the synapse. We studied synaptic connections at NMJ of the crayfish claw. These synapses have many resemblances to those of the mammalian brain. We have found that a relatively short period of nerve stimulation at high frequency produces a significant increase in the efficiency of synaptic transmission, named LTF. We determined that LTF is due to enhanced rate of release of neurotransmitter (NT), glutamate, which is secreted in a quantal manner from the nerve endings. Morphological data obtained from three-dimensional reconstruction using electron micrographs of the nerve terminal are being analysed in order to determine whether there exists a structural change which could account for the observed enhancement of NT release. However, by applying the binomial analysis it can be shown that there is an increase in both the probability of a quantum of NT being released and in the number of active synapses. Hence we can conclude that LTF is the result of alteration in the functional properties that are presynaptic in origin.

ACUTE HEPATITIS B INFECTION: EFFECT OF CLINICALLY SILENT HIV STATUS

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Both hepatitis B (HBV) and the human immunodeficiency virus (HIV) infections predominantly effect male homosexual and intravenous drug users. As HIV impairs the immune response, it may interfere with the host's ability to eradicate HBV. Hence we made a retrospective study of HIV status in patients with acute HBV infection followed to recovery. Fourteen males, 13 of whom were homosexual and 1 a heterosexual IV drug user, entered our study. All 14 cleared HBsAg within 3 months. Twelve developed anti-HBs but 2 remain with anti-HBc alone for up to 3 years following acute infection. Neither of the patients who failed to make anti-HBs were infected with HIV at the time of acute HBV infection and they have remained HIV negative up to the present time. However, 7 of the 12 who developed anti-HBs had S/N ratios of less than 10. Of these 7, 6 had HIV testing, 3 were positive.

These data show that HIV infected individuals are able to eradicate HBV when acutely infected. Low convalescent titres of anti-HBs, in some of the patients, were independent of HIV infection.

ENHANCED METABOLISM OF PHOSPHOLIPASE A_2 TREATED LOW DENSITY LIPOPROTEIN BY HUMAN ADIPOCYTES

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Evidence has accumulated that the recognition site for low density lipoprotein (LDL) on human adipocytes is different from the apoprotein B specific classical LDL receptor of cultured human skin fibroblasts. It has been suggested that lipoprotein phospholipids may play a role in fat cell-lipoprotein interactions. To test this hypothesis, LDL modified with phospholipase A_2 (PLA_2) was incubated with freshly isolated fat cells and fat cell plasma membranes to assess binding and catabolism.

LDL (d.1.024-1.045) was isolated from human plasma and incubated with various concentrations of cobra venom PLA_2. The modified LDL was reisolated and radioactively labelled. Extent of phospholipid hydrolysis was determined by measuring LDL lysophospholipid accumulation. Metabolic studies were then carried out using human fat cells and plasma membranes isolated from mediastinal adipose tissue of patients undergoing elective cardiovascular surgery.

PLA_2 treatment of LDL resulted in a particle which was similar to normal LDL in protein, cholesterol and triglyceride content but showed decreased phosphotidylcholine content and increased anodic migration on agarose gels. Modification of 16-46% of LDL phospholipids enhanced specific binding to plasma membranes up to 8 times normal at 37°C. Non-specific binding remained unchanged. LDL treated with PLA_2 in the presence of excess EDTA served as a control and did not show any compositional changes or enhanced binding to membranes. Incubation of PLA_2-treated LDL with intact fat cells indicated that LDL uptake and degradation were also increased significantly. These findings were replicable on tissue from both male and female subjects.

The results indicate that alteration of LDL phospholipids alters significantly LDL metabolism by human fat cells. This suggests a role for phospholipids in lipoprotein recognition. In a different context, the ability of human fat cells to bind and degrade PLA_2-treated LDL suggests that, unlike other mesenchymal cells, fat tissue may be involved in the metabolism of modified lipoproteins *in vivo*.

EFFECT OF SYNAPTIC NOISE ON THE POST STIMULUS TIME HISTOGRAM

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Cross correlations between the afferent inputs and the firings of a rhythmically discharging neuron have been used to estimate the effectiveness of a synaptic input and to derive some characteristics of the underlying post-synaptic potential (PSP). It is known that, in vivo, the transform between the PSP and its correlogram is largely dependent on the derivative of the PSP waveform, but there are results suggestive of an additional term in the transform which would be proportional to the PSP waveform. Computer simulation was used to determine how the cross-correlogram changes with varying noise waveform, noise frequency, and PSP waveform. Simulations with no noise showed the correlogram to be dependent only on the PSP waveform derivative, and simulations with significant noise produced a correlogram that was dependent on the PSP waveform itself. Analytic expressions for these transforms were derived. Intermediate noise levels did not yield a transform that was a linear combination of these extremes. The area under the correlogram peak, previously shown in vivo to be a good indicator of the strength of a synaptic connection, was linearly dependent on the noise level, and decreased markedly with increasing noise. These studies helped explain why in vivo correlograms are often wider than the underlying PSP rise time, and indicate that care must be taken when drawing conclusions about the strength of functional connections using cross-correlogram techniques, as these are very sensitive to noise levels.

AN EXPERIMENTAL TEST OF THE GABA HYPOTHESIS OF KINDLING: GENERALIZED SEIZURES IN CORTICAL- AND AMYGDALA-PREKINDLED RATS FOLLOWING ACUTE ADMINISTRATION OF GABA-COMPLEX AND ADENOSINE ANTAGONISTS

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The GABA hypothesis of kindling - as recently outlined by Burnham et al. - suggests that the development of secondary generalization in the kindling model is associated with a loss of GABA-mediated inhibition. If this is true, it follows that blockade of GABAergic function should produce secondary generalization even in subjects that have not been kindled.

The present study was designed to test this prediction of the hypothesis. Drugs were applied at appropriate intervals before the triggering of a focal seizure in a non-kindled animal, and electrographic and behavioural measures of secondary generalization were taken. Three different GABA complex antagonists were tested in a dose response paradigm: bicuculline, a specific antagonist for the GABA recognition site, picrotoxin, a drug that antagonizes GABA by binding to the associated chloride ionophore, and norharmane, a putative inverse agonist for the benzodiazepine receptor. In each case, the drugs were tested on both cortical and amygdala- implanted subjects, in order to assess possible differences related to the site of stimulation. For comparison, the adenosine agonist, aminophylline - already known to facilitate generalization in partially kindled subjects - was tested in the same paradigm. In line with the hypothesis, it was predicted that all GABA-complex antagonists would promote secondary generalization in prekindled rats.

Contrary to expectations, it was found that bicuculline and norharmane were ineffective at either site even at "near convulsant" doses. Picrotoxin was effective in facilitating generalization only in subjects implanted in the cortex. On the other hand, aminophylline was effective in promoting generalization in both the amygdala and cortically implanted prekindled subjects, although it was much more effective in animals with amygdala implants.

The failure of bicuculline and norharmane to produce "early trial" generalization raises serious questions about the GABA hypothesis of kindling. The contrasting actions of the different GABA complex antagonists raises corresponding questions concerning the current model of the GABA macromolecular complex.

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PREFERRED LOCALIZATION OF T. SPIRALIS IN MOUSE DIAPHRAGM

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Trichinella spiralis is a cosmopolitan nematode parasite of man and almost every other mammal. Infection occurs after ingestion of undercooked meat, usually pork, containing infective L1 stage worms. After maturation and mating in the intestine of the host, juveniles migrate via blood to skeletal muscle, where they transform it into a nurse cell. Using CD1 mice as a model host system, we studied the preferred localization of the worm in diaphragmatic muscle, and possible vascular alterations, such as new capillary growth, upon infection with the worm. By vascular perfusion of infected mice with dyed methyl methacrylate, we were able to observe at the light microscope level capillary networks around the nurse cells as well as carry out worm counts. Uninfected mice were perfused in an identical manner, and were used as controls in our assessment. The results of these studies suggest that a) the worm prefers peripheral regions of diaphragmatic muscle for nurse cell transformation and b) while the worm sets up its nurse cell, it does not appear to cause significant structural or organizational changes in muscle vasculature.

PARENTAL LANGUAGE PATTERNS IN AUTISM

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The special features of speech addressed to autistic children by their mothers and fathers were examined in an effort to clarify how the child's level of functioning and sex influenced parental language styles. Twelve children, six boys and six girls, half of whom were higher-functioning and verbal and the remainder lower-functioning and nonverbal were videotaped in a 15 minute interaction with their parents. A 14 category functional language coding scheme was employed to classify all parental language samples. Total number of utterances used were comparable for mothers and fathers but the mean length of utterance used by mothers was a function of the child's level of functioning while for fathers it was not. Mothers, but not fathers, employed shorter utterances and more prompts to produce speech when their children were lower-functioning and nonverbal than when they were higher-functioning and verbal. Higher-functioning, verbal and male children were given a greater number of prompts and questions, while lower-functioning, nonverbal and female children received more directives. Thus, both mothers and fathers of autistic children appear to be sensitive to their child's particular presenting characteristics, with mothers being superior in some respects.

IgE COMMITTED B CELLS FOLLOW A DISTINCT DIFFERENTIATION PATHWAY

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We recently described an IgE secreting, Epstein-Barr Virus (EBV) transformed B cell clone (K1D5), which co-expressed IgM, IgD and IgE. We have now asked whether this clone represents a rare or a common cell in the differentiation pathway leading to IgE expression. Cell sorting and limiting dilution analysis suggested that IgE committed, EBV-responsive B cells occur at a frequency of 1 in 1-3000 normal B cells and that they express surface μ, δ and, in 30% of cells, ε prior to virus infection and culture. Coincidence analysis of $>$1000 very low density limiting dilution cultures indicated that IgE production was invariably linked to IgM/IgD production but not to other isotypes throughout the entire culture period. On no occasion were cultures found that produced IgE alone. The co-expression of IgM/IgD/IgE was maintained throughout several sublining and cloning steps and in all subclones the amounts of μ and ε 7S heavy chain "units" were similar. These clones expressed normal sized mRNA, cytoplasmic protein of μ, δ and ε classes and showed vDJ-μ rearrangement on the expressed allele while ε classes and pseudo-ε genes were retained in germline configuration. We propose that IgE committed B cells invariably and stably co-express μ, δ, and ε. While co-expression of greater than one isotype may occur transiently in other B cell sublineages, it appears to represent the exclusive differentiation pathway for IgE producing cells.

SPONTANEOUS OTO-ACOUSTIC EMISSIONS IN HUMAN EARS

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Spontaneous oto-acoustic emissions (SOAEs) are low-level acoustic signals generated from the inner ear in the absence of external acoustic stimulations. The emissions are usually not audible, but can be detected by a sensitive microphone placed in the external auditory meatus, and identified as "spikes" above the -20 dB SPL noise floor on their frequency spectra. Not everyone has SOAEs, and if one has, they are not present at all times. In our experiments, we studied the distribution and the properties of SOAEs in human subjects. Of all the 47 subjects we tested, 15 of them (32%) had emissions, including 4 with multiple emissions. In terms of ears, 13 subjects had SOAEs in one ear, and 2 in both ears. The SOAEs span a frequency range between 1100 Hz and 2600 Hz (average around 1700 Hz); but each emission has a single frequency component, which shows little variation (less than 0.1%) with repeated measurements at different times. Interaction with external tones was demonstrated in some subjects. The emission shows a frequency-drift and an amplitude reduction when a pure tone of approximately the same frequency as that of the emission, or of great enough amplitude, is applied to the emitting ear. The correlation of SOAEs to tinnitus was also examined; of the 5 subjects who suffered from tinnitus, 3 had no measurable emissions; and for the "emitters", there was no evidence that the "ringing" they heard was identical to their SOAEs. However, 4 non-tinnitus subjects were able to pitch-match their "ringing" to within 1/6 octave of their SOAEs. The SOAEs seem to be audible in some cases and in extreme quiet.

ASSESSMENT OF A LINKED DNA MARKER FOR PRESYMPTOMATIC DIAGNOSIS OF ADULT POLYCYSTIC DISEASE IN NORTH AMERICA

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Adult polycystic kidney disease (APCKD) is a common autosomal dominant disorder which contributes to 9% of individuals on chronic dialysis. A recently described DNA probe, 3'HVR has been closely linked to APCKD in European families (Reeders et al. 1986 Nature 317:542). The purpose of this project was to assess the diagnostic reliability and accuracy of the 3' HVR probe for North American populations. This was done in collaboration with Reeders who generously provided the 3' HVR probe. Buffy coat DNA was extracted from the WBC of 12 members of 2 unrelated families, one English and one French Canadian by the standard methods. PVU II digested DNA was electrophoretically separated on 1% agarose gels, transferred onto nylon membranes, hybridized with 3'HVR and autoradiographed. Polymorphic DNA fragments of the size range (1-8kb) correlated with the clinical picture of APCKD. The recombination frequency between APCKD and the marker was 25% (2/8), slightly higher in our 2 families than previously reported for European populations (2-11%). There is no evidence for genetic heterogeneity. With the assessment of additional families to test the reliability of these findings, hopefully in the future the 3'HVR probe may be useful in the preclinical diagnosis of APCKD in N.A.

ROLE OF PREOPERATIVE TRANSCUTANEOUS FEMORAL ARTERIOGRAPHY IN POSTOPERATIVE COMPLICATIONS OF GROIN WOUNDS FOLLOWING ARTERIAL RECONSTRUCTION

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A prospective study is presented of the effects of preoperative transcutaneous femoral arteriography on bacterial contamination and postoperative wound complications of groin incisions in 44 arterial reconstructive procedures. Positive cultures occurred in 43.2% of patients and in 30.7% of the 88 groin incisions. There was no correlation found between presence of hematoma due to arteriography and subsequent positive groin culture. Higher incidence of positive culture did occur for patients who had a difficult arteriography or whose reconstructive procedure was longer than 4 hours.

Seven patients had postoperative groin wound complications, including 3 lymph leaks and 4 confirmed or suspected infections. There were no graft infections. No correlation was found between site of arteriography and site of wound complication. Neither positive culture nor difficult arteriography nor presence of hematoma were accurate predictors of postoperative wound complications.

Based on the lack of evidence to suggest that any facet of arteriography, save a difficult procedure, led to any predisposition to bacterial contamination or wound complication in the groins, it is concluded that transfemoral arteriography does not increase the risk of complications of arterial reconstruction involving a femoral anastomosis.

THE CONTINUOUS MEASUREMENT OF MOOD OVER TIME

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Accurate measurement of mood over time is a necessary prerequisite for the meaningful study of circadian rhythm and other biorhythms, such as those related to hormonal fluctuation, as well as for studies in cyclic affective disorder and psychosomatic disease. Recently, investigations into the mutual influences between the immune system and the neural system require even more sensitive ways to monitor mood from day to day and from hour to hour.

This paper reports on an instrument designed to measure mood on four dimensions of affect simultaneously: sad-happy, calm-anxious, low-high energy, and good-bad. These four dimensions form interleaving axis on a circular space. The person whose mood is being monitored traces their subjective assessment of mood on a trajectory in the circular mood space.

In order to determine sensitivity, reliability, and validity, thirty subjects were followed on a daily basis for eighty days each. Subjects completed a variety of standard mood scales as well as the mood circle. Results demonstrated that the mood circle is a practical, sensitive, reliable, and valid instrument for measuring mood on a continuous basis.

MULTICELL SPHEROIDS AS AN *IN-VITRO* MODEL OF TUMOUR PHOTODYNAMIC THERAPY

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Photodynamic Therapy (PDT), involving the use of the photosensitizer hematoporphyrin derivative (HPD) or its main tumour-localizing component dihematoporphyrin ether (DHE), in combination with high intensity red light, marks a significant advance in our ability to eradicate or control a variety of localized tumours. However, the details of the mechanism of action of this drug *in-vivo* remain to be elucidated. We have used multicellular tumour spheroids (MTS) of V-79 Chinese hamster cells as a three-dimensional tissue culture model of poorly vascularized nodular tumours, in order to study the role of a number of treatment and microenvironmental parameters in modifying the response of tumours to PDT. Intra-spheroid DHE uptake/distribution kinetics were examined by quantitative fluorimetry of extracted porphyrins, and by histology/fluoresence microscopy combined with automated image analysis and microdensitometry. PDT dose response studies, as a function of DHE concentration, light exposure, spheroid size and oxygen concentration, were carried out using the endpoint of regrowth delay. The results of these studies suggest that the direct photocytotoxic effect of DHE and light at depth within spheroids, and thus presumably within localized tumours *in-vivo,* may be limited by restricted DHE penetration and accumulation, as well as by internal hypoxia.

A BAYESIAN APPROACH FOR ASSESSING TOXICITY TO NEW DRUGS (D): GUILLAIN-BARRE SYNDROME (GBS) AND ZIMELIDINE (Z)

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The causality assessment of adverse drug reactions (ADRs) to new D is difficult. BARDI (Bayesian Adverse Reaction Diagnostic Instrument) assesses the causality of ADRs by decomposing the probability (P) of D causation into 6 quantities: the prior odds (based on background information) and 5 likelihood ratios (dealing with case information), and comparing these assuming D and non-D causation. We analyzed reports of Z-induced GBS. Z was given to approximately 14,000 patient-years over 16 months. Nine subjects developed GBS which led to Z withdrawal from the market. When BARDI was used to analyze the cases retrospectively, the Ps of Z-causation were high (range, P=0.978 to 0.997). Furthermore, analysis done using only information known at time of reporting suggests that these Ps would also have been high (range, P=0.76 to 0.97). These results suggest that Z caused GBS. Thus, BARDI may play a role in the evaluation of severe ADRs to new D, and may increase confidence in these assessments.

COMPARISON OF BLOOD-BASED AND ASANGUINOUS CARDIOPLEGIC SOLUTIONS ADMINISTERED AT 4°C: AND ULTRASTRUCTURAL MORPHOMETRIC STUDY IN THE DOG

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Although several studies have shown better myocardial preservation with blood-based than asanguinous cardioplegic solutions at myocardial temperatures above 15° C one might suspect blood to become unsafe at lower temperatures because of increased oxygen-hemoglobin affinity and viscosity. We compared myocardial preservation in dogs subjected to 6 hours of aortic cross-clamp and treated with either (Group I) modified Roe's asanguinous cardioplegia at 4° C, (Group II) blood cardioplegia at 4° C, or (Group III) blood cardioplegia at 27° C (4 dogs per group). All dogs regained adequate heart function after 20 minutes of reperfusion, and tetrazolium staining showed no gross evidence of infarction in any heart. However, semi-quantitative analysis of changes in myocyte ultrastructure and morphometric analysis of mitochondrial swelling revealed signs of more severe injury in Group I than Groups II or III (P=0.005). These analyses showed equivalent myocardial preservation in Groups II and III. We conclude that blood cardioplegia is as safe and effective at 4° C as at 27° C, and that blood cardioplegia is safer and more effective than asanguinous cardioplegia at 4° C.

THE PATHOLOGY OF AIDS: TGH EXPERIENCE

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The autopsies of 44 patients who died of the acquired immune deficiency syndrome (AIDS) were reviewed. All the patients were male, 36 were homosexual, 1 was a homosexual and a drug abuser, 4 were bisexual and 3 involved blood transfusions. The ages ranged from 21 to 60 years (mean = 38.7 years). The most common diagnoses at autopsy were disseminated cytomegalovirus in 26, Kaposi's sarcoma (KS) in 16, *Pneumocystis carinii* pneumonia (PCP) in 13 and atypical mycobacterium in 11. Cytomegalovirus infection of organs involved the lung, adrenals, CNS, GI and spleen. The skin was the most frequently involved with KS, followed by lung, GI and lymph-nodes. PCP was diagnosed clinically in 33 cases but only 13 had persistent PCP at autopsy. Conversely, atypical mycobacterium infection was diagnosed in 2 cases clinically, but 11 cases demonstrated atypical mycobacterium infection at autopsy. CNS pathology was demonstrated in 37 of the 44 cases examined. Cytomegalovirus encephalitis and toxoplasmosis were the most common CNS infections (10 and 5 cases respectively).

Cryptococcosis meningitis and progressive multifocal leukoencephalopathy were seen in 2 and 1 case respectively. Lymphoma was diagnosed in 3 cases and the most frequent cerebrovascular complication was infarction seen in 8 cases. The results of this study further demonstrate that regional differences do exist (which are not well documented at present) in the frequencies of opportunistic infection, pathologies and risk factors involved with AIDS, and that it may be important to the clinician to be knowledgeable of these factors for the recognition and understanding of the evolution of the syndrome indigenous to the geographical region of his or her area of practice.

THE EFFECT OF INSULIN ON TRIGLYCERIDE AND APOPROTEIN SECRETION BY THE LIVER

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It was previously shown that chronic exogenous insulin administration enhances triglyceride (TG) production *in vivo*. It is not yet clear whether this is due to a direct effect on the liver or whether it reflects some other process occurring in the hyperinsulinemic (HI) state. *In vitro* studies have reached divergent conclusions. Hence we have undertaken to examine the production o-VLDL-TG by the livers of two-week HI rats. This was accomplished by measuring the key lipogenic enzymes in, and the rate of VLDL-TG secretion during perfusion of livers of such rats. Two groups of rats served as controls; chow controls were fed chow only; sucrose controls were fed chow and had ad lib access to a 10% sucrose drinking solution. Sucrose supplemented diet increases the activity of lipogenic and glycolytic enzymes and inhibits the key enzyme of gluconeogenesis. This enhances TG synthesis and the secretion of larger particles. The infusion of insulin does not further change the activity of these enzymes. However, it does result in an increase in the number of particles secreted .by enhancing apoprotein secretion. This results in more remnants which have been shown to have atherogenic potential.

CLONING OF THE 112K RAT MYOBLAST "TRIGGER PROTEIN" GENE

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Cloning of the gene for a 112 Kda rat L6 myoblast "trigger protein" was undertaken. The "trigger protein" is believed to be involved with triggering hexose transport in L6 myoblasts. The myoblasts were grown in glucose-free conditions to increase the number of hexose transport carriers present. Total cellular RNA was isolated, and the poly (A)+ RNA fraction was selected by using an oligo(dT)-cellulose column. A cDNA:mRNA hybrid was synthesized from the poly(A)+ fraction using M-MLV reverse transcriptase. Double stranded cDNA was then synthesized from the hybrid using DNA Polymerase. Eco R1 linkers were added to the ds cDNA, and the ds cDNA were incorporated into lambda gt11 vectors. The lambda gt11 were packaged into a viral coat and adsorbed into *E. coli* Y1090 (r-) hosts for expression. The fusion protein products were detected by immunoblotting with anti-L6 PMV antibody. The positive clones were isolated and the cDNA insert was removed by restricting with Eco R1. Examination of the DNA by gel electrophoresis revealed a 2000 base pair cDNA fragment which is believed to code for part of the "trigger protein". The protein product of the cDNA fragment is presently under investigation.

STIMULATION OF FEEDING IN THE RAT BY CENTRAL INJECTIONS OF rhGRF IS A SHORT-TERM AND PHOTOPERIOD-SENSITIVE EFFECT

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We have previously reported the ability of intracerebroventricular (icv) injections of rat hypothalamic growth hormone-releasing factor (rhGRF) to facilitate feeding in rats through a central mechanism which appears to be separate from GRF's classic role as an inducer of growth hormone secretion by the anterior pituitary. To date however, all studies of GRF's role in feeding have focused on eating during the less active, light photo-phase of rats circadian feeding cycle. The present studies therefore examined possible variations in rhGRF's effect on feeding with respect to light versus dark feeding states.

In the first study forty male rats received 4 consecutive daily icv injections of rhGRF (4.0 picomole) or saline administered during either light or dark photoperiods. Results indicated that rhGRF injections administered during the light consistently increased 90-minute but not 24-hour eating relative to vehicle treated animals. rhGRF injections during dark photoperiods tended to suppress eating for 90-minute but not 24-hour intake. In an attempt to further characterize these light-dark differences in rhGRF's effect, a dose-response study was undertaken in which 20 male rats were given icv injections of 0, 0.4, 4 and 40 picomole doses of rhGRF during either light or dark photoperiods. Injections during the light produced a dose-dependent facilitation of 90-minute feeding whereas those given during the dark resulted in a dose-dependent inhibition. Again 24-hour intake was unaffected.

These results suggest that rhGRF's ability to influence eating is restricted to short intervals following injections and that the effect is dependent on the photoperiod studied. This latter point raises the possibility that rhGRF may be involved in the mechanism responsible for circadian eating in the rat. Further support for this notion comes from recent evidence from our lab that rhGRF injections into the SCN, a hypothalamic site which receives GRF terminals and is involved in regulation of many circadian behaviours, results in dramatic increases in feeding.

COMPARING TECHNIQUES OF NERVE FIBRE MORPHOMETRY

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In order to determine the accuracy, precision, and statistical validity of quantitative measurements of axon and fiber sizes in transverse sections of peripheral nerves, three approaches to computerized planimetry were compared.

Using drafting equipment, a mock photomicrograph and microscopic section, each with 100 identical "fibres" of known dimension, were constructed. Diameters and areas for the 100 fibers on the photomicrograph were measured 10 times using three methods: 1) circular approximation from minimum diameter, 2) circular approximation from orthogonal diameters, and 3) calculation of diameter and area from a digitized circumference. Analogous data was collected from the mock section using a microscope and camera lucida attachment. Data variance was evaluated with respect to a) differences between measurement methods and b) as a function of sample size.

Preliminary analysis of fiber diameter data revealed a significant learning effect with repeated data collection. Although, sample variance was smallest for data collected using a circular approximation of orthogonal diameters, no significant differences in variance were found among methods. A minimum sample size of 200-300 fibers was required to achieve a stable variance. This data may suggest that the different methods compared are equivalent.

PREVALENCE OF LOW LACTOSE DIGESTION IN CANADIAN-BORN CHINESE

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There is debate whether lactose digestion capacity (LDC) in humans is clinically influenced by environmental conditions. This was studied by comparing Canadian-born Chinese (CBC) with existant data on Singapore-born Chinese (SBC) since both share similar genetics but differ in cultural environments. Fifty CBC volunteers were each given a lactose load and the lactose breath hydrogen test was performed by analyzing end-expiratory breath samples for their hydrogen content which is indicative of the amount of undigested lactose. Forty-nine subjects (98%) had a low LDC, which is statistically similar to existant data on the SBC. A genetic basis for low LDC is therefore supported; an environmental influence, if present, was not large enough to have been detected by this experiment. An incidental finding was that males had a significantly higher LDC than females ($p<0.001$) in the CBC population studied.

SENSORY POTENTIAL OF COMMONLY USED DONOR TISSUE FOR TRANSFER

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After reconstructive surgical techniques are used rehabilitation of the hand is greatly improved when a course of sensory re-education is followed. It has been shown that after using toe pulp transfers to reconstruct fingertips, the average static two-point discrimination at the repair was nearly normal for that site. However, the sensory potential of the tissue at the donor site is not known. It may be possible to improve the acuity of discrimination of normal, undisplaced donor tissue by a short course of sensory re-education. We tested this hypothesis in a random control study using a subject population of 20 healthy people. Each subject was randomly assigned to either a control or experimental group. Those in the experimental group were instructed to educate 4 specific sites out of the 8 sites used in the study which are commonly used in tissue transfers; bilaterally, the plantar surface of the great toe, the first dorsal toe web space, the first dorsal hand web space, and the area of skin superficial to the subject's radial pulse. The side (right or left) of each site that the subject trained was randomized. The training and testing included static and moving two-point discrimination and timed object recognition. All subjects were tested prior to the study and at 1 week intervals for 3 weeks by one investigator who was blinded as to the subject's group assignment. Results are pending.

DEFINITIVE EXTERNAL FIXATION OF PELVIC FRACTURES

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Since 1976, 39 patients at our centre have had stable and unstable pelvic fractures treated by external skeletal fixation. These patients were reviewed in order to evaluate external fixation as a definitive mode of treatment of pelvic fractures.

Patients were examined for pain and deformity, and changes in lifestyle were evaluated. Charts and radiographs were reviewed to classify initial fracture pattern and degree of reduction. Average follow up was 3 years (1-7.5). 80% of patients had fixators applied in the first 2 days following injury; average duration of fixation was 9 weeks (6-20). Average time to full weightbearing was 3 months. 24% had manipulation of their fixator due to loss of reduction; 16% had fixators removed due to pin tract infection.

24 patients had stable fracture patterns with posterior elements intact (18 anteroposterior compression and 6 lateral compression); 15 had unstable vertical shear injuries. 83% of AP crush, 67% of lateral compression and 27% of vertical shear fractures had acceptable reductions. Patients with acceptable reductions had better long term results at follow up than those with unacceptable reductions of similar fracture patterns. Stable fracture patterns had better results than unstable ones. Incongruity of the articular surfaces of the sacroiliac joint predispose it to degenerative change, often accompanied by disabling low back pain. We feel that internal pelvic fixation should be considered if acceptable reduction cannot be obtained or maintained, especially with unstable shear type fractures through the sacroiliac joint.

CHARACTERIZATION OF A NOVEL MOUSE HSP70 GENE

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The heat shock (or HSP70) genes are the most highly conserved genes in biology and they serve as an elegant means to study the mechanisms underlying the regulation of gene expression. Members of the mouse HSP70 multigene family possess highly homologous coding sequences yet display different modes of transcriptional regulation. Some of the mouse genes are expressed in all cells, some are only transcribed in response to stress, and others are developmentally regulated. Members of the mouse multigene family were isolated by screening a genomic lambda library and two clones were selected for further study. Detailed physical maps of the mouse DNA inserts of these clones were constructed by restriction mapping and Southern analysis. Our results reveal that the two genomic DNA inserts differ in size (14kb and 23kb) and orientation but that they overlap and both contain an HSP70 gene on a 3.8kb EcoR1 fragment. This EcoR1 fragment was purified and subcloned into the plasmid vector pUC18 and the resultant recombinant plasmid (pSB003) was used to sequence most of the coding region of the gene by the dideoxy method using double-stranded DNA. The gene does not contain introns and the predicted amino acid sequence resembles, but is not identical to that constitutively expressed members of the multigene family. The 5′ regulatory sequence of the HSP70 gene was subcloned separately and partially sequenced. The gene contains regulatory elements common to all HSP70 genes as well as unique sequences suggesting a different mechanism of transcriptional regulation. RNA from a variety of mouse tissues was probed with pSB003 DNA and a 2.5kb transcript of this gene (now called hsc70B) was detected in the testes. It appears that this novel member of the HSP70 multigene family is the gene previously known to be transcribed in spermatids and to encode a protein found on the surface of active spermatozoa.

EFFECTS OF ALLOPURINOL ON MYOCARDIAL ISCHEMIC INJURY INDUCED BY CORONARY ARTERY LIGATION AND REPERFUSION

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The effects of allopurinol pretreatment (1 mg/ml in drinking water for 7 days) on biochemical and morphological changes following left circumflex coronary artery ligation (40 min) and reperfusion (60 min) were examined in pentobarbital-anesthetized rabbits. During the ischemic phase, allopurinol pretreatment provided significant preservation of sarcolemmal and mitochondrial ATPase activity and myocardial ATP levels as compared with untreated animals. During the reperfusion phase, allopurinol pretreatment significantly prevented the decrease in left ventricular pressure, of sodium and calcium accumulation, and decreased the incidence of cardiogenic shock and ventricular fibrillation as compared with untreated animals. Among the subcellular organelles examined morphologically, allopurinol had preferential protective effects on the mitochondria both during the ischemic and reperfusion phases. Our study suggests that the preservation of mitochondrial and functional integrity by allopurinol may be an important determinant of its protective actions in myocardial ischemic/reperfusion injury.

EFFECT OF REFRACTORINESS ON THE ELECTRICAL CONTROL ACTIVITY OF GASTROINTESTINAL SMOOTH MODEL — A COMPUTER APPROACH

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Variations in refractoriness of gastrointestinal (GI) smooth muscle can effect the electrical control activity (ECA) and therefore SGI motility. A computer model which has the capacity to study refractoriness in GI smooth muscle has been proposed by Dr. B.L. Bardakjian - "The Mapped Clock Oscillator Model for Smooth Muscle Electrical Activity". A population of cells with identical intrinsic properties is assumed to be represented by one oscillator. By using a two oscillator configuration, the model can be employed to study the effect of refractoriness on such parameters as entrainment frequency and phase lag between the ECA of two coupled populations of GI smooth muscle cells. An increase in the refractory period of one population caused (i) a decreased ECA entrainment frequency of the two populations of cells and (ii) a trend of increasing ECA phase lags between the two populations. Results suggest that an alteration in the refractory period of one population of cells, when coupled to another population, has an effect on both populations even though the refractory period of one population has not been altered. The synchrony of gastric oscillators is known to be governed by intrinsic properties such as frequency and resting membrane potential as well as coupling mechanism. This study suggests that in addition, refractory properties may have a significant role in causing gastric dysrhythmias.

SOME SPINAL CORD CIRCUITRY IN MAN

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The connections from large muscle afferents (group Ia fibers) to motoneurons of certain limb muscles have been examined in the cat and baboon. The circuitry reflects the functional relationships of these muscles. We investigated the equivalent circuitry in man by examining changes in firing probabilities of single, voluntarily activated motor units, which can provide information about EPSPs and IPSPs in these motor units. Muscles were stimulated with low threshold electrical or mechanical stimuli and single motor unit recordings were taken. A computer was used to generate a peri-stimulus time histogram from which firing probabilities were deduced and analyzed for information about the connections in question. The long head of biceps femoris (BI), semitendinosus/-semimembranosus (ST), vastus medialis (VM) and vastus lateralis (VL) were examined. All muscles showed homonymous facilitation. Heteronymous facilitation was easily demonstrated between the two vasti muscles. There was no demonstrable heteronymous facilitation from ST to BI. No unequivocal statement could be made regarding connections from BI to ST. Inhibition (presumed to be reciprocal inhibition) was shown when stimulating the femoral nerve and recording from the hamstring muscles. No such inhibition was demonstrable from BI afferents to quadriceps motoneurons, and in only a few studies did afferents from ST inhibit quadriceps motoneurons. This study determined the physiological state of these connections in man. These findings resemble the circuitry in the baboon more closely than the circuitry in the cat, likely reflecting the differing functions of these muscles between species.

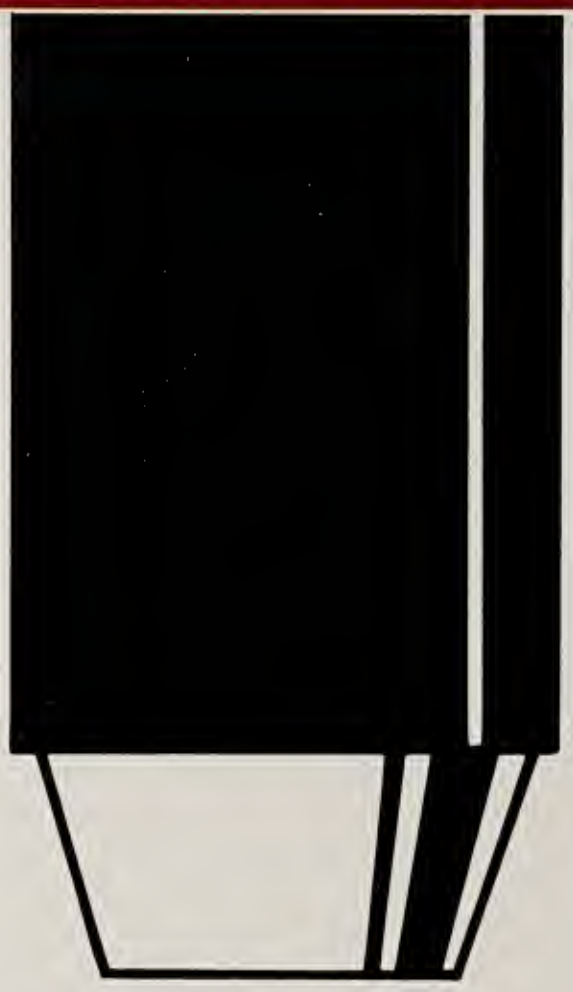
(continued from S-2)

be an expert teacher you not only need in depth knowledge but also the ability to think on the spot. This requires a 'turned-on mind'.

What is the relevance of this 'turned-on mind' to students preparing to become physicians? Pretend that you are a general practitioner in a rural setting. A patient presents to you an unusual symptom complex. First you create a useful hypothesis in terms of a differential diagnosis. You are challenged to investigate the problem without the aid of a CT-scan or radioimmunassay. In this setting it is not the thousands of memorized (and partially forgotten) facts but your ability to think through the problem that is most important. Without a 'turned-on mind' you are lost. As well you learn to rely on the expertise of other health care personel such as nurses and technicians. Much of the ongoing education of this staff depends on your expert knowledge and ability to teach.

A small proportion of medical students, often with graduate degrees, decide to pursue a career in research. In medicine they develop a new way of asking scientific questions. It isn't just the search for biological truth that draws their curiosity, but the discovery of disease mechanisms. Many of these individuals are the future clinical and basic science investigators of our medical schools. Let us hope that they will teach with their minds turned-on.

Bravo to the participants of Research Day 1987!



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Undergraduate Medical Student Research Day